Br. J. clin. Pharmac. (1984), **18**, 535–539

Influence of food and reduced gastric acidity on the bioavailability of bacampicillin and cefuroxime axetil

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1 The present study was designed to investigate the effect of food and of a raised intragastric pH on the bioavailability of two prodrug β-lactam, antibiotics, namely bacampicillin and cefuroxime axetil.

2 Six healthy volunteers participated in an intraindividual comparison of absorption of (a) prodrug, (b) breakfast, followed by prodrug, (c) breakfast, ranitidine and sodium bicarbonate followed by prodrug, and (d) ranitidine and sodium bicarbonate, followed by prodrug. All volunteers were dosed with both bacampicillin and cefuroxime axetil under the above regimens. The drug-free periods between trials were 7 days.

3 Blood samples were obtained before and 20, 40, 60, 90, 120, 150, 180, 210 min and 4, 5, 6, 8 and 10 h after administration. The urine was collected for a period of 10 h after dosing with the antibiotic. An estimation of the relative bioavailability of the drugs under the various regimens was made by comparing the average areas under the serum concentration time curves and also the amounts recovered in the urine.

4 Both food and reduced gastric acidity decreased the bioavailability of bacampicillin (as ampicillin) and these variables had an additive lowering effect on the AUC and percentage urinary recovery. Possibly this ester becomes partially hydrolyzed prior to absorption on raising the intragastric pH. Adsorption onto food components or complexing with proteins may also play a role in the reduced bioavailability of bacampicillin in the presence of food.

5 In contrast, the absorption of the cefuroxime ester was enhanced postprandially. This may be rationalized in terms of delayed gastric emptying and gastrointestinal transit which allows more complete dissolution or prolonged residence at the most favourable site of absorption in the intestine. However, the raising of the intragastric pH by the concomittant administration of ranitidine and sodium bicarbonate, reduced the enhanced postprandial absorption. Possibly the good absorption of cefuroxime axetil requires a sufficient low gastric pH to allow the drug to dissolve in the gastric juices.

Keywords bacampicillin cefuroxime axetil gastric acidity food bioavailability

Introduction

Welling (1977) has presented a comprehensive and critical review of the literature concerning the influence of food and diet on gastrointestinal drug absorption. He also pointed out that volunteers who participate in bioavailability studies invariably receive the drugs when they are in a fasting state, so that their blood level and urinary excretion profiles are obtained free of interference due to food or other agents.

The results of an earlier trial (unpublished data) showed a significant increase in absorption of cefuroxime axetil when the dose was taken 0.5 h after a meal rather than with the meal. This could have been due to neutralization of gastric acidity by the food. In order to assess the effect of a reduction in gastric acidity a follow-up volunteer study (unpublished data) showed a significant decrease in the mean urinary recovery of cefuroxime after predosing with ranitidine.

The esterification of the carboxyl group of a β-lactam antibiotic with a radical invariably leads to increased lipid solubility. This prodrug approach cloaks many drugs with a mantle of new physical and chemical properties which substantially improves absorption. The active forms are readily regenerated by enzymatic cleavage within the body. Pivampicillin, an ampicillin prodrug, has been found to have a considerably reduced absorption in the presence of food (Fernandez *et al.*, 1973). In contrast, the ampicillin precursor hetacillin is absorbed somewhat better when dosed with meals (Jusko & Lewis, 1973).

The majority of studies demonstrate that food has an inhibitory effect on gastrointestinal drug absorption. Many factors e.g. solid or hot meals and acidic molecules, delay gastric emptying (Welling, 1977) and as most drugs are optimally absorbed from the small intestine the potential exists of delaying the absorption of an orally dosed drug. The mechanisms causing increased absorption of certain drugs have been rationalized, but not proven, in most cases (Welling, 1977). One explanation suggested for increased absorption is that delayed stomach emptying permits more drug to dissolve in the stomach before it passes into the optimal absorption environment of the small intestine (Bates *et al.*, 1974).

The gastrointestinal absorption of many drugs has been shown to be altered by concomitantly administered antacids (Hurwitz, 1977). In mice, peak serum ampicillin levels were depressed more than 50% by concomitant administration of magnesium hydroxide with the antibiotic, whereas the effects of aluminium hydroxide, magaldrate (hydrated magnesium aluminate), calcium carbonate and sodium bicarbonate were slight and inconsistent (Hurwitz *et al.*, 1973). When using sodium bicarbonate the potential effects of very high concentrations of electrolytes within the gastrointestinal tract influencing the dissolution of drug products should be considered. Antacids may bind drugs or alter gastrointestinal tract motility but the H_2-receptor antagonist ranitidine is not known to affect muscular tone. On increasing the intragastric pH, hydrolysis of up to 30% of ampicillin esters (i.e. pivampicillin and carampicillin) occurs prior to absorption (Swahn, 1976), thus reducing bioavailability.

In the present study the influence of food and of gastric acidity on the bioavailability of two prodrug β-lactam antibiotics, namely bacampicillin and cefuroxime axetil was examined by regimens allowing pre- and postprandial administration of the drug with and without the concomitant administration of ranitidine and sodium bicarbonate.

Methods

Six healthy ambulatory volunteers, two females, four males, mean age 21.6 years and mean weight 70.5 kg, were the subjects. None had cardiac, hepatic or renal disease. The protocol had been approved by the Ethical Committee of the University of Pretoria and the volunteers gave their written consent.

A cross-over experimental design was followed allowing at least 1 week interval between treatments. The volunteers fasted overnight, at least 10 h before the test and were permitted to eat no food apart from test meals, until 4 h after dosing. The treatments were as follows:

Day 1:
300 mg ranitidine $\xrightarrow{115\ min}$ 4 g $NaHCO_3$ $\xrightarrow{5\ min}$ 1600 mg bacampicillin $\xrightarrow{2\ h}$ breakfast

Day 2:
1600 mg bacampicillin $\xrightarrow{2\ h}$ breakfast

Day 3:
300 mg ranitidine $\xrightarrow{85\ min}$ breakfast $\xrightarrow{30\ min}$ 4 g $NaHCO_3$ $\xrightarrow{5\ min}$ 1600 mg bacampicillin

Day 4:
Breakfast $\xrightarrow{35\ min}$ 1600 mg bacampicillin

Day 5:
300 mg ranitidine $\xrightarrow{115\ min}$ 4 g $NaHCO_3$ $\xrightarrow{5\ min}$ 1 g cefuroxime axetil $\xrightarrow{2\ h}$ breakfast

Day 6:
300 mg ranitidine $\xrightarrow{85\ min}$ breakfast $\xrightarrow{30\ min}$ 4 g $NaHCO_3$ $\xrightarrow{5\ min}$ 1 g cefuroxime axetil

Day 7:
1 g cefuroxime axetil $\xrightarrow{2\ h}$ breakfast

Day 8:
Breakfast $\xrightarrow{35\ min}$ 1 g cefuroxime axetil

Breakfast was made up of standard components (e.g. orange juice, milk, sausage, rolls and cheese) and the tablets were washed down with 250 ml water. The sodium bicarbonate was also dissolved in 250 ml water.

Ampicillin and cefuroxime levels in serum were monitored by taking blood samples before administration and at the following times after dosing: 20, 40, 60, 90, 120, 150, 180, 210 min and 4 h, 5 h, 6 h, 8 h and 10 h. The serum was separated by spinning at 3000 rev/min for 5 min and then decanted into a bijou bottle to be stored at −18°C until assay. The urine was collected for a period of 10 h after dosing with the antibiotic. The volume was measured and one 20 ml aliquot, for ampicillin or cefuroxime assay, was taken and frozen.

Assay of serum and urine samples

The ampicillin and cefuroxime were assayed by RP h.p.l.c. using a 25 cm 5 μ ODS column. Isocratic elution was used in both cases. The mobile phase for ampicillin was 8% methanol; 2% acetonitrile: 90% 0.05 M ammonium di-

Table 1 Mean (± s.e. mean) serum levels (mg/l) and bioavailability parameters (C_{max}, t_{max}, and $AUC_{0-10\ h}$) for respectively, bacampicillin and cefuroxime axetil following oral administration under four different regimens. Percentage urinary recovery from 0–10 h is also listed

Time (h)	*Bacampicillin (1.6 g)*				*Significant*
	D1	*D2*	*D3*	*D4*	*(0.05 level)*
0.33	1.60±0.62	6.55±1.97	0.87±0.40	1.51±0.67	
0.66	6.10±1.53	9.34±1.33	1.05±0.39	4.51±1.83	
1.0	6.47±1.58	12.30±2.09	1.40±0.50	6.50±1.74	
1.5	5.08±1.12	10.15±1.63	1.55±0.48	6.51±1.24	
2.0	3.59±0.69	7.90±1.27	1.39±0.38	5.37±0.95	
2.5	2.48±0.42	5.75±1.04	1.20±0.29	4.64±0.64	
3.0	1.72±0.28	4.27±0.66	1.07±0.25	3.89±0.41	
3.5	1.20±0.20	3.28±0.44	0.85±0.21	3.28±0.32	
4.0	0.85±0.16	2.17±0.31	0.50±0.13	2.52±0.16	
5.0	0.44±0.11	1.06±0.15	0.38±0.09	1.79±0.19	
6.0	0.28±0.07	0.54±0.06	0.31±0.06	1.28±0.19	
8.0	ND	0.14±0.02	0.18±0.02	0.54±0.15	
10.0	ND	ND	ND	0.34±0.14	
C_{max} (mg/l)	0.858±0.028	0.923±0.090	1.405±0.319	1.667±0.227	4>1,2
t_{max} (h)	6.610±1.633	12.188±1.959	1.692±0.478	6.138±1.408	2>1,3,4
$AUC_{(0-10h)}$ (mg l^{-1} h)	13.587±2,592	29.912±4.687	4.885±1.093	22.043±2.856	2>1.3
% urinary recovery	17,580±2.652	40.625±7.100	11,372±2.414	33.295±4.472	2>1,3
Time (h)	*Cefuroxime axetil (1.0 g)*				*Significant*
	D1	*D2*	*D3*	*D4*	*(0.05 level)*
0.33	1.55±0.24	0.00	1.89±0.78	0.55±0.47	
0.66	2.56±0.58	2.49±0.75	4.04±0.99	5.73±1.61	
1.0	3.63±0.62	5.45±1.18	5.95±0.42	9.93±1.90	
1.5	3.95±0.76	7.62±1.09	6.38±0.36	13.47±1.16	
2.0	3.57±0.62	8.44±0.93	5.73±0.40	12.53±1.10	
2.5	2.94±0.49	8.03±0.75	5.72±1.01	10.64±1.07	
3.0	2.35±0.36	7.23±0.56	4.75±0.99	9.17±0.73	
3.5	1.86±0.25	6.29±0.40	4.14±0.97	6.58±0.77	
4.0	1.46±0.18	5.37±0.27	3.07±0.80	4.98±0.64	
5.0	0.91±0.11	3.78±0.17	1.35±0.21	2.99±0.41	
6.0	0.57±0.09	2.60±0.18	1.15±0.39	1.50±0.30	
8.0	0.24±0.05	1.20±0.18	0.42±0.17	0.44±0.14	
10.0	0.13±0.03	0.55±0.14	0.29±0.10	0.19±0.08	
C_{max} (mg/l)	1.192±0.141	2.072±0.177	1.460±0.152	1.542±0.098	2>1,3,4
t_{max} (h)	4.315±0.653	8.573±0.879	7.277±0.793	13.558±1.035	4>1,2,3
$AUC_{(0-10h)}$ (mg l^{-1} h)	13.437±1.424	35.705±2.791	23.447±2.869	39.822±2.911	4>1,3
% urinary recovery	12.345±1.833	39.810±4.376	30.530±3.834	61.298±7.714	4>1,2,3

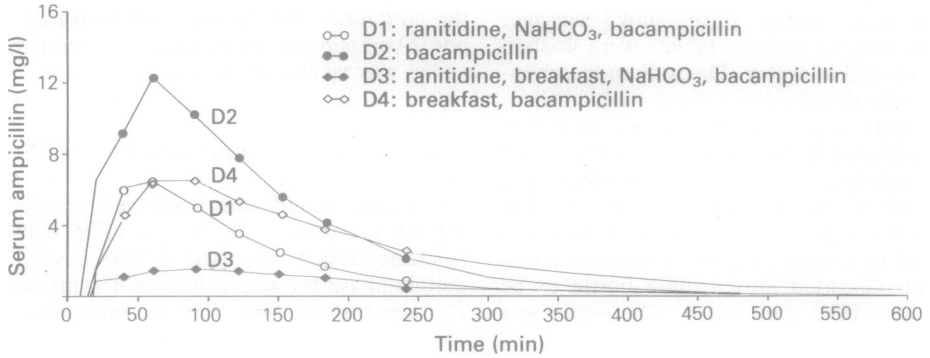

Figure 1 Mean serum concentrations after administration of bacampicillin (1.6 g).

hydrogen phosphate buffer with a flow rate of 2.5 ml/min whilst that for cefuroxime was 11% acetonitrile: 89% of the same buffer at a flow rate of 2.5 ml/min.

The effluent was monitored spectrophotometrically at 210 nm and 273 nm for ampicillin and cefuroxime respectively.

Interpretation of results

The ampicillin and cefuroxime concentrations in serum were plotted against time, and the time of peak concentration (t_{max}) and the peak concentration (C_{max}) were assessed by conventional methods. The area-under-the-curve (AUC) was calculated by the trapezoidal rule. The concentration determined in the urine was multiplied by the volume of urine excreted to obtain the total percentage recovery of the unchanged drug. In respect of each of these parameters the daily values were compared by means of the Kruskall-Wallis test, an analysis of variance and Duncan's multiple range test.

Results

The mean serum levels for both drugs under the four different regimens as well as for C_{max}, t_{max}, AUC- values and percentage urinary recovery, with the statistical analysis are given in Table 1. The mean concentrations of ampicillin (rendered by oral bacampicillin) are given in Figure 1 while that of cefuroxime is presented graphically in Figure 2. An estimation of the relative bioavailability of the drugs under the various regimens was made by comparing the average areas under the serum concentration-time curves and also the amounts recovered in the urine.

It seems clear from Figure 1 that both food and reduced gastric acidity tended to lower the bioavailability of bacampicillin (as ampicillin) and that these variables had an additive lowering effect on the AUC and percentage urinary recovery.

In contrast, the bioavailability of cefuroxime was considerably increased by postprandial administration. Furthermore the concomitant

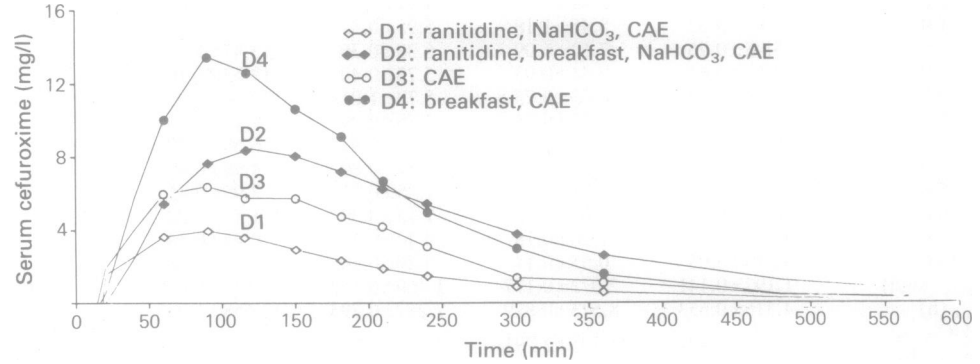

Figure 2 Mean serum concentrations after administration of cefuroxime axetil (CAE, 1.0 g).

reduction in gastric acidity with the addition of ranitidine and sodium bicarbonate manifested with a delay in the shape of the serum-drug profile and a reduction in C_{max}, but the AUC_{0-10h} was not significantly reduced. The percentage urinary recovery, however, dropped from 61.3% to 39.8%. The areas under serum level curves from 0 to 10 h after dosing were consistently lower in fasted subjects and were even more depressed when fasted subjects were pretreated with ranitidine and sodium bicarbonate.

Discussion

In man the concurrent administration of aluminium hydroxide gel or magaldrate had no effect on ampicillin absorption (Hurwitz *et al.*, 1973). The bioavailability of ampicillin was also not altered by concomitantly administered cimetidine (Rogers *et al.*, 1980). However, the serum levels of ampicillin were both delayed and reduced by food (Neu, 1974) and the extent of reduction was independent of dietary components (Welling *et al.*, 1977).

In the present study a standard cooked breakfast markedly enhanced the bioavailability of cefuroxime, but considerably reduced that of bacampicilin. This altered bioavailability can hardly be explained in terms of changed metabolism since biotransformation has only a very limited role in the elimination of β-lactam antibiotics.

The enhanced absorption of the cefuroxime ester may be rationalized in terms of delayed gastric emptying and gastrointestinal transit which allows more complete dissolution or prolonged residence at a site in the intestine from which absorption is optimal. Since pretreatment with ranitidine and sodium bicarbonate resulted in a lower bioavailability for cefuroxime axetil compared with that of the fasting state and also tended to cancel the enhanced postprandial absorption, it is probable that good absorption of cefuroxime axetil requires a sufficiently low gastric pH to allow the drug to dissolve in the gastric juices.

The greatest reduction in overall bacampicillin bioavailability was in the presence of both food and reduced gastric acidity. However, a raised intragastric pH and the post-prandial state each had a marked inhibitory effect in their own right. The most likely explanation is that ths ester becomes partially hydrolyzed prior to absorption when the gastric acidity is buffered by food or reduced by pretreatment with a H_2-receptor blocker and antacid. An alternative, or additional, explanation could be that food may influence bacampicillin absorption more directly because of its adsorption onto food components or complexing with proteins. Acid neutralization may also inhibit tablet disintegration or drug dissolution.

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(Received February 17, 1984, accepted May 20, 1984)